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EXAMINER	
JOHNSON,N	

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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☐ Responsive to communication filed on _____ ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☒ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☒ Claims 1-18 are pending in the application.
   Of the above, claims 17,18 are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1-16 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☒ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

1. Applicant's election without traverse of Group I, claims 1-16 in Paper No. 6 is acknowledged.

2. Claims 17 and 18 are withdrawn.
Claims 1-16 are pending.

3. This application has been filed with informal drawings which are acceptable for examination purposes only. Formal drawings will be required when the application is allowed.

4. The drawings are objected to because the subfigures of Figures 1-4 must be separately labeled. Correction is required.

5. The disclosure is objected to because of the following informalities:

> The subfigures of Figure 4 are labelled 4(1)-4(4), while subfigures for Figures 1-3 are labelled with arabic letters.
>
> Subfigures 1A-1F, 2A-2B, 3A-3B and those in Figure 4 are not separately described in The Brief Description of Drawings.

Appropriate correction is required.

6. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to provide an enabling disclosure without complete evidence either that the claimed biological materials are known and readily available to the public or complete evidence of the deposit of the biological materials.

The specification lacks complete deposit information for the deposit of the hybridoma cell line CNCM Accession No. I-1397. It

is not clear that hybridoma cell lines and monoclonal antibodies possessing the identical properties of I-1397 and the monoclonal antibodies that it secretes are known and publicly available or can be reproducibly isolated from nature without undue experimentation.

Exact replication of a cell line is an unpredictable event. Although applicant has provided a written description of a method for selecting the claimed hybridoma cell lines and monoclonal antibodies, this method will not necessarily reproduce antibodies and hybridomas which are chemically and structurally identical to those claimed. It is unclear that one of skill in the art could derive antibodies and hybridomas identical to those claimed. Undue experimentation would be required to screen all of the possible antibody and hybridoma species to obtain the claimed antibodies and hybridomas.

Because one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed in the absence of the availability of the claimed hybridoma cell line and monoclonal antibody, a suitable deposit of the cell line for patent purposes, evidence of public availability of the claimed cell line or evidence of the reproducibility without undue experimentation of the claimed hybridoma, is required.

Applicant's referral to the deposit of I-1397 on page 7 of the specification is an insufficient assurance that all required

deposits have been made and all the conditions of 37 CFR 1.801-1.809 met.

If the deposits are made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposits have been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposits will be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced if viable samples cannot be dispensed by the depository is required. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

If the deposit is not made under the provisions of the Budapest Treaty, then in order to certify that the deposits comply with the criteria set forth in 37 CFR 1.801-1.809 regarding availability and permanency of deposits, assurance of compliance is required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has the authority and control over the conditions of deposit over his or her signature and registration number averring:

(a) during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request:

(b) all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application:

(c) the deposits will be maintained in a public depository for a period of at least thirty years from the date of deposit or for the enforceable life of the patent of or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material, whichever is longest; and

(d) the deposits will be replaced if they should become nonviable or non-replicable.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If deposits are made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the cell line described in the specification as filed is the same as that deposited in the depository, stating that the deposited material is identical to the biological material described in the specification and was in the applicant's possession at the time the application was filed.

Applicant's attention is directed to In re Lundak, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR 1.801-1.809 for further information concerning deposit practice.

7. Claims 3-4, 7-8, 11-12 and 14-15 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

8. The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to provide an enabling disclosure. The specification does not adequately teach how to make and use the claimed antibodies as broadly claimed. Those of skill in the art would not know how to effectively make and use the claimed methods with a reasonable expectation of success based on the teachings of the specification and the evidence of record.

a. Claims 1-3, 5-7, 9-11, 13-14 and 16 are drawn to monoclonal antibodies that bind to any unspecified antigen on B lymphoblastoid cells. The specification exemplifies only one such monoclonal antibody, the BAT-1 monoclonal antibody, in support of the broad claims. This antibody recognizes a 48-50 kD protein, increases thymidine incorporation in human peripheral blood lymphocytes (p.19), induces cytotoxic lysis of tumor cells (p.22) and exhibits an anti-tumor effect in the model systems of lung metastases of MCA fibrosarcoma, B16 melanoma and 3LL tumor cells in the C57BL and BALB/c mice (see p.27). The nature of the antigen recognized by antibodies of the invention is presumably critical in terms of the immunostimulatory property of the

exemplary antibody. One can not extrapolate from the single antigen-antibody system disclosed to the production of immunostimulatory antibodies that bind to other B lymphoblastoid cell antigens. The specification provides no direction or guidance with respect to the identification of antibodies having different antigen-binding specificities which have immunostimulatory properties without undue experimentation.

b. Claim 1 is broadly drawn to "immunostimulatory" antibodies. The specification exemplifies antibodies that mediate only the specific immunostimulatory effects previously discussed in paragraph 8a above. Absent a more specific and detailed description in applicant's specification of how to effectively identify the immunostimulatory antibodies, undue experimentation would be required to make and use the claimed invention with a reasonable expectation of success.

c. Claim 10 is broadly drawn to a method for the treating a "disease or disorder." The specification does not teach how to treat diseases or disorders commensurate with the scope of the claim. While the specification contemplates that the diseases or disorders to be treated according to the claimed methods include HIV infection, various autoimmune diseases and some genetic and acquired immunodeficiencies (p.8, lines 21-26), it does not teach how to effectively treat HIV-1 infections, various autoimmune diseases and genetic and acquired immunodeficiencies. The only <u>in vitro</u> working example exemplified in the specification is

directed to the treatment of tumors in experimental mice. This example can not be extrapolated to HIV-1 infection and autoimmune diseases, which differ widely in their etiologies and pathobiology. The class of diseases which are broadly categorized as autoimmune diseases includes numerous diseases of diverse underlying etiologies and disease mechanisms, whose pathologies are complex and, in most cases, incompletely understood. Thus, the specification does not set forth sufficient teachings to allow one skilled in the art to practice the claimed invention with a reasonable expectation of success. One of skill in the art could not predict the efficacy of the claimed methods for treatment of diseases or disorders other than the murine lung metastasis model on the basis of the evidence of record.

d. Claims 1, 2 and 10 are drawn to the treatment of tumors and cancer, and can be broadly interpreted to read on the treatment of human tumors. The present invention pertains to the experimental and unpredictable area of the in vivo treatment of human tumors by the administration of immunoglobulins. The difficulties associated with the development of effective antibody-based therapies for human cancers are well established in the art. The example provided in the specification, the anti-tumor effect of the claimed monoclonal antibodies in the model systems of lung metastases of MCA fibrosarcoma, B16 melanoma and 3LL tumor cells in the C57BL and BALB/c mice (see p.27) does not

provide sufficient basis to predict the efficacy of the disclosed method for the treatment of human tumors.

The specification provides insufficient evidence that the claimed methods are effective for treatment of human tumors. The claimed invention has been exemplified in methods of administering the claimed monoclonal antibody to tumor-bearing mice. However, as evidenced by Osband and Ross (Immunology today 11:193-195, 1990), the mouse is not an art-recognized animal model which is predictive of the efficacy of immunotherapeutic agents in humans. Osband and Ross teach that the response of animals of immunotherapy is not predictive of their effects in human patients. Due to the extreme complexity of the host-tumor immunorelationship, animals to not fully mimic the biology of human patients with cancer and the immune systems of animals and humans differ such that immunotherapeutic agents fail to demonstrate comparable activity in animals and humans. (See the paragraph bridging page 192-193). Those of skill in the art would not predict the ability to effectively use the claimed methods for treating human tumors on the basis of the evidence of record.

e. Claim 16 is drawn to an agent other than the claimed monoclonal antibody which is capable of enhancing the activity of the cytotoxic lymphocytes, or broadly interpreted, enhancing the immunostimulatory effect obtained in claim 1, in a synergistic manner. The specification teaches only the one such agent, Il-2

(p.22). No description of the physical, chemical or pharmacological characteristics of such other agents is provided. Absent a specific and detailed description in the specification of how to effectively make and use the agents as broadly claimed undue experimentation would be required to practice the claimed methods with a reasonable expectation of success.

9. Claims 1-16 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

10. Claims 1-16 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claim 1 is vague and indefinite in the recitation of "immuno-stimulatoy." It is unclear whether activation and/or proliferation of lymphocytes or other immuno-stimulatory effects are claimed. Thus the metes and bounds of the claim are unclear.

b. Claim 1 and 2 are vague and indefinite in the recitation of "elicits anti-tumor effect." Tumors have many biological and pathological effects. For example; growth in mass, metastases, cachexia and angiogenesis. the particular anti-tumor effect claimed is unknown. Thus, the metes and bounds of the claim are unclear.

c. Claim 2 recites an improper Markush group. The applicant is referred to MPEP § 706.03(y) and advised to reformat the claim to read "wherein R is a material selected from the group consisting of A,B,C and D," or "wherein R is A,B,C, or D."

d. Claims 3, 7, 11 and 14 are vague and indefinite in the recitation "having the characteristics of." The specific characteristics referred to are unknown.

e. Claim 9 is vague and indefinite in the recitation "disease or disorder." The particular diseases or disorders to be treated with the claimed antibodies are not known. How a disease differs from an disorder is unknown.

f. Claim 16 is vague and indefinite in the recitation "an agent other than said antibody." The identity of the agents other than said antibody id unknown and thus, the metes and bounds of the claim are unknown.

g. Claim 16 is vague and indefinite in the recitation "the cytotoxic lymphocytes," which lacks antecedent basis.

h. Claim 16 is vague and indefinite in the recitation "enhancing the activity of," as it is unclear what specific activities are enhanced.

11. Claim 16 is objected to because of the following informalities: the recitation "an an" is apparently a typographical error. Appropriate correction is required.

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 1-2, 5-6, 9-10, 13 and 16 are rejected under 35 U.S.C. § 102(b) as being anticipated by Brown et al. (Blood 73:651-661, 1989). Brown discloses a monoclonal antibody for anti-tumor uses that is the same as that claimed in claims 1-2, 5-6, 9-10, 13 and 16. This monoclonal antibody is obtained by immunizing an animal with B lymphoblastoid cells, binds to B Lymphoblastoid cells and induces proliferation and activation of peripheral blood lymphocytes (p.655, column 2, two patients made an immune response against mouse immunoglobulin after administration of the monoclonal antibody, which is immuno-stimulation). Brown also discloses the hybridoma cell line that produces said monoclonal antibody, the strong anti-tumor effect of said monoclonal antibody and the use of the monoclonal antibody with other agents capable of enhancing its activity, in this case Il-2.

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or

on sale in this country, more than one year prior to the date of application for patent in the United States.

15. Claims 1-2, 5-6,9-10, 13 and 16 are rejected under 35 U.S.C. § 102(b) as being anticipated by Ledbetter (U.S. Patent No. 5,182,368, January 26, 1993). Ledbetter discloses an immunostimulatory monoclonal antibody for anti-tumor uses that is the same as that claimed in claims 1-2, 5-6, 9-10, 13 and 16. This monoclonal antibody is obtained by immunizing an animal with B lymphoblastoid cells (col.8, lines 63-67), binds to B Lymphoblastoid cells and induces proliferation and activation of peripheral blood lymphocytes (abstract). Ledbetter also discloses the hybridoma cell line that produces said monoclonal antibody, the use of said monoclonal antibody for the treatment of diseases and disorders (col.4, lines 17-26) including anti-tumor treatments (col.4, lines 27-42), a pharmaceutical composition containing the monoclonal antibody (see col.16, lines 51-54) and the use of the monoclonal antibody with other agents capable of enhancing its activity (see col.13, lines 20-27).

16. Claims 3-4, 7-8, 11-12 and 14-15 are rejected under 35 U.S.C. § 102(b) as anticipated by or, in the alternative, under 35 U.S.C. § 103 as obvious over Ledbetter (U.S. Patent No. 5,182,368, filed May 24, 1991). For this analysis, the recitation in claim 3, "having the characteristics of the monoclonal antibody produced by the hybridoma cell line ... CNCM No.I-1397," is broadly interpreted to be a monoclonal antibody with the same

physical properties as those disclosed in the specification for CNCM No.I-1397, also called the BAT-1 Mab. That is, a monoclonal that identifies a binds a 48-50 kD protein (p.7) on cells of B lineage. Ledbetter discloses an immunostimulatory monoclonal antibody, that recognizes a polypeptide of approximately 50 Kd (see p.18, lines 45-46), with the properties previously discussed in paragraph 15, above that is the same as that claimed in claims 3.

17. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

18. Claims 3-4, 7-8, 11-12, 14-15 are rejected under 35 U.S.C. § 103 as being unpatentable over Hoskin et al. (Cancer Immunol. Immunother. 29:226-230, 1989) in view of Ledbetter. Hoskins et al. teaches the use of an immunostimulatory monoclonal antibody to induce proliferation and activation of peripheral blood lymphocytes. This antibody, when injected into tumor-bearing mice, elicits an anti-tumor effect (see abstract). Hoskins does not teach an antibody that recognizes a 50 Kd protein on B lymphoblastoid cells. However, the teachings of Ledbetter, disclosing an immunostimulatory monoclonal antibody that recognizes a polypeptide of approximately 50 Kd (see p.18, lines 45-46), have been previously discussed in paragraph 15 above.

It would have been *prima facia* obvious to one of ordinary skill in the art at the time the claimed invention was made to substitute the monoclonal antibody taught by Ledbetter in the anti-tumor method taught in Hoskins et al. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Hoskins, that the *in vivo* activation of cytolytic cells with anti-tumor activity by antibodies holds potential as an alternative form of cancer treatment (p.229).

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nancy A. Johnson, Ph.D. whose telephone number is (703) 305-5860. The

examiner can normally be reached on Monday-Friday from 8:30-5:00. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marian Knode, can be reached on (703) 308-4311. The fax number for the group is (703) 305-7401. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

N Johnson

Nancy A. Johnson, Ph.D.

February 22, 1996

PAULA K. HUTZELL
PRIMARY EXAMINER
GROUP 1800